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The Present Status of Cancer Investigation.

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I am presenting this review of the subject, which is wholly abstracted from current literature on the subject, in the absence of Dr. Gilman, who is detained at home by illness.

Etiology. Injury and chronic inflammation seem to bear an almost constant relation to cancer. Not crushing injuries or single severe injuries, which are more likely to be followed by sarcoma, but repeated slight injury or irritation. Examples of this are shown in smokers' lip cancer; X-ray cancer of the hands in people constantly exposed to the rays; X-ray cancer developing from lupus after X-ray aplications; tar and asphalt workers' cancer, referred to by Oliver; chimney sweeps' cancer of scrotum (Oliver, Butlin), 29 of the 32 cases in one London Hospital being in sweeps; bladder cancer in analine workers (Leyberth); gallbladder cancer in 70 per cent. of cases associated with gall stones, and nearly 3 to 1 more common in women, just as gall stones are; epithelioma in carbon workers (Leuke); cancer in sailors following dermatitis from exposure (Unna); cancer of neck from rope injury, among natives of the Philippines who carry heavy burdens supported by rope around the head and neck (Gilman); Bilharzia carcinoma; cancer of the abdominal wall from the use by natives of India of small earthernware stoves held next to the abdomen; breast cancer in women, particularly after chronic mastitis (Leaf); pyloric cancer on ulcer base (McCarty and the Mayo brothers, Moynihan and others); uterus cancer, more common after cervical injury and inflammation (Cullen); betel leaves cancer of inner side of cheek in persons chewing the leaves, always on side where stuff is stored in the mouth.

Of negative value, is absence of cancer of penis in Jews and Mohammedans, both of whom practice circumcision, and therefore chronic balinitis the common etiological factor is rare. In 100 cases of cancer of the penis in the Massachusetts General Hospital, not one in a Jew, and Bashford has never seen it in a Mohammedan.

There are three interesting ideas regarding the growth of cancers that are worth mentioning, since there is argument to support each one.

1st. Substances exist under extreme or unusual conditions of the body that stimulate cell proliferations. (Spuda, Loeb, Fischer, Starling).

2nd. Substances normally present in the body affording protection vs. unusual cell proliferation may be absent temporarily or permanently (Beard, Leyden and Bergall).

3rd. Cancer cells have a greater proliferative quality because they have a greater attraction to nutritive material (Albrecht and Erlich).

In regard to the first hypothesis Conheim's views form the basis. He argues that tumors arise from cells "that in the course of development have been displaced from their normal relationship, or have failed to undergo a normal atrophy." He is able to show such groups of cells in both infant and adult bodies, and calls them "embryonal rests." They have been found very commonly by some observers, and the natural question arises as to why some and not others of these "rests" are awakened into proliferative activity, and under what conditions are they so awakened.

Cancer cells as such do not exist; they are merely ordinary epithelial cells possessed of a dynamic force which either causes them to grow unusually when normal epithelium does not grow in the same way, or causes them to be influenced by nutritive conditions in a way that normal cells are not influenced. Pathologists have shown us many facts that are interesting in this connection. First, the normal fertilized ovum in the human being, if lodged elsewhere than in the uterus, is a parasite growing at the expense of its host, invading the tissue of the fallopian tube, for example, just like a cancer, until finally it eats its way through, and the too often fatal results follow. Second, Gibbons has shown chronically inflammed glands in Hodgkin's disease actually invading the walls of blood vessels, that is, breaking through basement membrane and invading the tissues of the host like cancers. Third, Loeb found that injuring the uterine wall in pregnant guinea pigs, led to proliferation of decidual tissue at the point of injury. This does not occur if the corpora lutea is removed before injury. Fourth, Starling found that virgin rabbits injected subcutaneously with rabbit embryo emulsion show an hypertrophy of the mammary glands, and rabbits that have borne young show lactation in addition to this.

The second hypothesis, that there is frequently absent from the body substance which when present serve a protective function, and that in this absence cell proliferation may result under favoring excitation, has also some facts to support it, for example the altered nutrition of a part frequently injured or irritated. The possible neutralization of substances needed for protection vs. invasion of cells by products of decomposition resulting from injury as in cancer of the breast or by chemical substances causing the irritation, as in cancer of the stomach. The use of normally protecting cells for other purposes because of the irritated conditions of the part in question. It is hard to explain the complete absence of digestive fluid from the stomach in the presence of some cancers involving very small areas. Beard's use of trypsin and amylopsin in the treatment of cancer is along this line of reasoning.

Erlich's idea, the basis of the third hypothesis, of a greater affinity of cancer cells over normal for nutritive substances, brings us back to the question of the dynamics that makes one epithelial cell normal and the other a part of a cancer.

Immunity Experiments. Immunizing against cancer in animals, especially mice, has brought up a close study of the relation of cytolysis and of anaphylaxis to this end. It has been shown that an animal sensitized to one organ of another species develops in his blood a substance which when injected into an animal of the species from which the organ was taken, will cause necrotic changes in that organ. An example of this is seen in Beebe and Rogers' serum for exophthalmic goitre. Any foreign proteid, when injected into a living animal, sensitizes that animal to that particular proteid, so that a second injection of enough of the same proteid, harmless as the initial injection may have been, may cause the death of the animal. Vaughn, Pierce and Anderson and others have shown the extent to which this may be carried and it is now well understood that cytolytic sera is specific for the animal species furnishing the cells and not necessarily for any special type of cell from the animal. About this fact there is, however, still some doubt.

Erlich's studies led him to believe that the artificial immunity to tumors in lower animals was not blasto-specific, but Bashford showed definitely that it was the epithelial covering of the embryo alone which produced immunity in mice against epithelial tumors. Von Dungern described a specific epitheliolysin in the serum of rabbits previously injected with ciliated epithelium from the trachea of the cow, and suggested the possibility of developing sera for different epithelial cells. This, however, has thus far been unsuccessful, and attempts to produce a specific antiserum for cancer have been unsuccessful.

Among the more recent investigations upon immunity to tumors, those of von Dungern and Coca, "Zeitschrift fur Immunitatsforschung und experimentelle Therapie. Vol. 11, 24 Mar., 1909, p. 391," are perhaps the most significant in their bearing upon the problem of immunization against cancer in human beings.

Von Dungern excised a young, rapidly growing, moderately malignant sarcoma, which had been derived originally from a wild hare, and had been transplanted to the laboratory rabbit, and inoculated with it two groups of rabbits. Group A consisted of normal, i. e., hitherto unused animals, group B had been previously inoculated with an emulsion of an identical tumor derived from another transplant. Among the second group were animals in which the tumor resulting from the first inoculation was still present as well as animals in which the resulting growth had been excised, or had been spontaneously absorbed, and also animals in which the first inoculation had failed altogether. Although every individual of group A developed large tumors, in not one animal of group B was the second inoculation successful. Furthermore, the tumors still present in some of the members of group B, which were derived from primary inoculation, softened after the second injection of tumor material, and were converted into sterile abscesses.

There is considerable question as to what is the exact explanation for the disappearance of the sarcoma in von Dungern and Coca's original experiments published in 1909. Whether there be a protective function exercised by basement membrane, or a definite cytotoxin produced in the blood, is a matter of controversy. In the one case, the disappearance of the tumor would be practically by starvation, the body being fortified against this parasitic action of the tumor. The other hypothesis supposes a selective and specific cytotoxin with destructive power for cancer epithelium and not for normal epithelium.

Imperial Cancer Research Fund Report.—Notes. Lancet, July 23, 1910, page 265.—Emphasis placed on the immediate influence of irritation. Experimental sarcoma produced "from what have been the non-malignant connective tissues of carcinoma." Occurrence is rare and has been noted in only two strains of transplantable carcinoma, one strain showed the change in only a small number of animals and was only completed after several repeated transplantations. In the other the transformation was more frequent and rapid, and occurred at times in one transference. Transplantations of spontaneous tumors in the same animal are almost invariably successful, but in other animals of the same species they frequently fail whether the inoculated animals are young or old, healthy or cancerous. For illustration, in 55 re-inoculations of cancerous animals with their own tumors 54 were positive; 77 inoculations of spontaneous tumors in other spontaneously affected mice only 5 were positive. (American observers have met generally with a larger percentage of successes). Bashford's experiments would seem to show that the cancer cell was much more dangerous to the host than to other individuals.

Young animals furnish more suitable soil than older ones, and it is definitely shown in propagating tumors that the general biological properties show a relative constancy, but occasionally there are changes difficult to account for. "All cancerous mice do not exhibit an equally suitable soil for tumors in general. Spontaneous variations of the parenchyma cells of tumors during propagation suggest that we have a repetition, in a minor degree, of the cellular processes responsible for the primary transformation of non-cancerous into cancerous tissue. Just as cellular changes occurring during propagation may transform a slow-growing tumor into one rapidly proliferating, so in the tissues prior to cancerous growth the responsive proliferation of cells may pass into the progressive, independent proliferation of cancer."

Successful vaccination against cancer does not prevent the development of spontaneous cancer.

Methods successful in preventing or retarding the growth of transplantable tumors have been without effect in the growth of spontaneous tumors.

Thirty-four strains were examined for spirochetes with negative results. Reference is made to the fact that they have been found in mice without tumors.

Regarding immunization Bashford claims that resistance can be induced only by employment of living tissue. No success has been obtained by him through disintegration of cancer cells of providing for the continuance of the powers of inducing resistance and at the same time destroying its power of growth.

Bashford records the failure of the experiment in 25 spontaneous tumors to prevent recurrence or dissemination or prevent successful re-inoculation of spontaneously affected animals with their own tumors.

Notes from the Philippine Journal of Science, January, 1910.—Von Dungern and Gorowitz experiments show the development of hyper-sensitiveness to cancer proteids in the patient with cancer. There is an increased reaction from subcutaneous inoculation with extract from the patient's own tumor, whereas in healthy individuals no reaction occurred, nor was there any increased reaction in the patients injected with extracts from the tumors of others. It has been repeatedly shown that the organism can be sensitized against its own tissues even to the point of destroying them, and these experiments of Gorowitz would seem to indicate that a cancer case may be sensitized against its own tumor.

Immunization in human beings.—Von Leyden and F. Blumenthal (Deut. Med. Woch., 1902, 28-36), attempted to produce active immunity in a cancer patient against his own cancer, by injecting into the patient some of the tumor tissue of which he was the host. In three instances they regarded that they had averted metastases and caused reduction in the size of affected glands.

Von Dungern and Ranzi have conducted similar experiments with cancer patients; Ranzi using carbolized extracts of their own tumor tissue.

Vaughn has reported a number of cases treated with small amounts of tumor material injected every three or four days, without proving anything further than a possible influencing of the original growth. He discusses the question from the point of view of a possible sensitization of the patient against his own tumor by injection into him of material from a similar tumor in another case, pointing out that a round-celled sarcoma was favorably influenced when used on another patient where it had failed as an autogenous vaccine.

Gay (Boston, Med. & Sug. Jr., Aug. 28, '09) from animal experiment showed that during what he termed the premetastatic period, the resistance of the individual could be increased by reinoculation of the tumor or products of it, to such an extent as to cause resorption of the original tumor. Gay further points out in the Harvard Cancer Commission lecture of 1909 that this premetastatic period lasted about 35 days. If the second implantation was made after this period, both it and the first implantation continued to grow. These experiments were controlled and corresponded to the findings of Bridre, Gaylord and especially Stricker.

Tyzzer, Harvard C. C. Lectures, 1909, p. 6.—After filtration of an emulsion of tumor tissue through ordinary filter paper, the inoculation of the filtrate has been attended (in animals) with negative results. If the tissue of inoculable tumors is kept at room temperature on its removal from the body, it soon loses its property of producing tumors on inoculation, and this change takes place still more rapidly if incubated at body temperature.

Secondary transplantation of tumors has been shown to be preventable by a preliminary inoculation of normal mouse tissue. Rapidly growing tumors of transplantory growth or slow growing tumors have known tendency to spontaneous absorbation. In many of these cases there is even cure of the original tumors where the possibility of spontaneous cure could have been excluded. Bashford warns that this result cannot be obtained in the case of spontaneous tumors, and adds, "Still more emphatically do we warn against applying to the human subject methods which after long perseverance have

enabled us to arrest the growth and even to cure animals of transplanted tumors."

The following points being definitely established by various investigators, a more complete incorporation of cancer material into a vaccine seemed justified as an experiment:

First: The second inoculation of tumors in mice in which the first plant had grown, had a distinct destructive effect upon the first plant, and in turn disappeared itself.

Second: Cancer is not transferable in animals however susceptible they may be, if the inoculated material is kept for some time outside the body even if kept at body temperature. The danger therefore of reproducing cancer is very small and no instance is reported among surgeons where cancer has followed injury of the surgeon's hands by cancer-contaminated instruments.

Third: There had been noted by a good many observers the definite influence on cancer tissue where extracts and emulsions of other cancers had been injected into the patient with cancer.

Gilman and Coca, recognizing all these facts and the hitherto experimental work on human cases, determined therefore in a series of inoperable carcinomas, to try the effect of an emulsion of the whole tumor, thus including in their therapeutic agent all that could possibly be included in the various extracts which had been tried by others, as well as any virtue that might lie in the body of the cell itself. Their initial report may be found in the Philippine Journal of Science, January, 1910. It gives some encouraging results in the relief of pain and cachexia and shows that in some cases where parts of the inoperable tumor were removed after treatment, that some degenerative changes had taken place.

Discussion.—H. A. L. Ryfkogel: Dr. Brown has gone over the subject so thoroughly that there seems to be nothing to add, except that he failed to mention some experiments of Blumenthal. I have seen in one of the recent numbers of the Medizinsche Klinische Wochenschrift a report on some of the experimental work performed by Blumenthal on some implantation tumors of rats. In 1904 he also published an article of similar work on carcinoma of rats, in which the disappearance of the carcinoma was caused by means of heteralogous vaccine. A rat with a rectal carcinoma was injected with an emulsion made from a carcinoma of another rat, the result being a cure. More recently he has made some studies on sarcoma of the rat, and found that it would disappear when treated by vaccine, and he also was able to treat it by a thoroughly autolyzed vaccine, and in this way claimed to have entirely destroyed the possibility of producing new inoculation tumors such as occurred in some of the cases treated by Gilman's method. He found that autolyzed vaccine was of no use after 21 days; that after 8 days it was not as active as it had been immediately after its preparation. His method of preparing the vaccine consists of grinding up the tissue as Dr. Gilman does, then shaking it thoroughly with several times its volume of chloroform water and incubating it for 72 hours. He found that in the animals upon which this autolyzed vaccine was used, that in no case did it produce inoculation tumors, although the original tumor injected did produce tumors. He found that if this autolyzed vaccine was injected into animals in which the same growth had been thoroughly established, that the tumor rapidly softened and disappeared. He tried no human cases with this method.

THE STATUS OF OUR VACCINE WORK IN CANCER.

By P. K. GILMAN, M. D.

Following experimental work, more particularly that of Van Dungern with whom one of us, Dr. Coca, worked for some months, we determined to apply to the human the methods of "vaccine" treatment in carcinoma that has been tried with various results on lower animals.

In an attempt to secure a "vaccine" against a malignant growth, we used various methods of preparation; extracts of tumors, infusions, and differently prepared comminuted malignant tissue. We decided finally that a "vaccine" prepared as follows gave the best results:

"About 15 to 20 grams of carcinomatous tissue is divided as fully as possible with a sharp pair of sterile scissors, then run through a vaccine grinder which gives a pulpy material of even consistence. The addition of a ccm of glycerin before passing the material through the grinder greatly facilitates the passage through the machine. The resulting pulp is shaken up in 20 cc of sterile saline solution and centrifugated for a few moments at a low speed to throw down coarse connective tissue fibres. The supernatant fluid is decanted with the ground carcinoma cells, enough 5% carbolic acid is added to produce a 0.5% solution, and after standing 4 to 6 hours the dose of vaccine is ready to inject."

Injection of the entire amount is made into the subcutaneous tissue; we have used the tissue of the abdominal wall, care being taken to so distribute the fluid as to avoid tension.

The extra malignant tissue we have stored until needed, keeping it sterile in a solidly frozen condition. Some tumors have been kept for 6 months before being used to prepare a "vaccine."

In a series of cases in Manila we have administered such a "vaccine," the cases embracing practically all stages of carcinomatous disease, from early operable cases through possibly operable to absolutely inoperable cases in the last stages.

The injection of the "vaccine" is followed in the majority of the cases by a local, as well as a general reaction. Locally there occurs about the point of injection a painful swelling; the skin is from 24 to 48 hours becoming quite firmly indurated and tender. If there is not too great tension or if there are present no micro-organisms, the swelling lessens in another 24 hours, and gradually subsides, losing its angry appearance and tenderness. Complete absorption may be slow, a more or less firm nodule persisting for several days. This, however, has always finally disappeared, leaving no palpable residue. Some of the masses have progressed to suppuration, the product of the breaking down, however, being sterile, and probably the result of too great tension at the time of inoculation. In but one or two cases have micro-organisms been obtained from the contents of such an "abscess."

The general reaction which has occurred in fewer of the cases, and upon which we do not at present lay great emphasis, consists in a rise in temperature of from 2 to 4 degrees, a general feeling of unrest and malaise, headache and at times slight chilly feelings. These symptoms usually come on about the second day, and subside the day following.

In each case in our series has an operation been done, and it has been just as thorough an operation as the condition of the disease allowed and the condition of the patient permitted. In those patients of the series where a prognosis was favorable, and the disease apparently eradicated, time only will show the result.

In a second group also when an operative cure was possible, though not probable the same test must be waited for.

In the cases which were inoperable, where definite carcinomatous material was necessarily unremoved at operation, the results of repeated injections of "vaccine" at intervals of two weeks have been instructive.

In brief, cachexia is in practically every case cleared up in a great degree following the injection of "vaccine" in three to five days. The mental condition of the patient is improved, the pain—if present—is lessened, the patient has a better appetite, the color of the mucous membranes improves. This change is marked in a very large majority of the cases and only in those patients who cannot "react," being too far gone, has it failed to follow the use of "vaccine."

About the seventh or eighth day following the injection, a change is noted in the carcinoma tissue